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Pharmacological Approaches to the Management of Cognitive Dysfunction in Schizophrenia

Philip D. Harvey[1] and *Margaret M. McClure*[2]

1 Department of Psychiatry, Mount Sinai School of Medicine, New York, New York, USA
2 VA VISN3 Mental Illness Research, Education, and Clinical Center, Bronx, New York, USA

Contents

Abstract

Cognitive dysfunction is a core feature of schizophrenia as deficits that are present in the majority of patients with schizophrenia frequently precede the onset of other symptoms and persist even after other symptoms have been effectively treated. The use of atypical antipsychotics has produced some small improvements, although the need for adjunctive treatment specifically targeting cognitive dysfunction is gaining widespread acceptance. Animal models and some small clinical trials have yielded results that are promising but not definitive. Psychosocial interventions have also met with some success in ameliorating some cognitive limitations. The mixed results of pharmacological interventions are most likely to be as a result of a combination of methodological flaws of many studies, poor outcome measures, dose administration effects and problems with the agents themselves.

Cognitive dysfunction is a core feature of schizophrenia as deficits that are estimated to occur in 75–85% of patients with the illness,[1] precede the onset of other symptoms in most patients[1] and

persist even after other symptoms have been effectively treated.[2] Although Kraeplin[3] identified the relationship between cognitive deficits and schizophrenia almost a century ago in his description of dementia praecox, effective treatments for these abnormalities have remained elusive.

Cognitive abnormalities as measured with standard neuropsychological measures are not clearly linked to positive symptoms,[4] which are often the most apparent and widely targeted for intervention; however, they are related to several other important features and aspects of the illness. Cognitive deficits are the single best predictor of functional outcome in schizophrenia.[5] Furthermore, cognitive deficits predict poorer medication[6] and treatment compliance,[7] reduced adaptive and social skills,[8] and increased tendency for relapse in first-episode patients.[9]

First-generation pharmacological interventions for schizophrenia, although effective in treating positive symptoms of the disorder, offered little relief for cognitive dysfunction. The widespread use of second-generation or atypical antipsychotics has offered some benefit in this area,[10] although the use of specific pro-cognitive interventions as adjunctive treatment agents is now widely accepted as a necessary next step in effectively treating cognitive limitations.

In this article, we review the profile of cognitive deficits within the schizophrenic population, as well as adjunctive treatments specifically addressing these abnormalities. We also discuss possible reasons for the lack of effect seen in current empirical examinations of pharmacological agents and offer suggestions for future research.

1. Profile of Cognitive Dysfunction in Schizophrenia

Individuals with schizophrenia perform worse than healthy individuals across a broad range of cognitive domains. There is variability within individual patients, although these cognitive abnormalities are relatively stable over time with what appears to be an increase in the normally expected decline in cognitive functioning later in life.[11-13] Cognitive dysfunction frequently precedes the onset of other symptoms,[1] and thus treatment,[14] and appears to remain largely unchanged even when other symptoms are in remission.[15] Generally, individuals with schizophrenia exhibit mild to moderate impairment in most cognitive domains, with more focal severe impairments in tasks that require working and episodic memory and executive functioning.[16,17] Specific cognitive deficits frequently observed in individuals with schizophrenia include difficulty with attention, concentration, memory, verbal skills, visual skills and problem-solving skills.[7-9,18] In addition, individuals with schizophrenia exhibit a significant impairment in working memory,[19] a weakness that has been hypothesised to underlie the broad range of deficits within this population.

The wide range of cognitive deficits within this population was one of the driving forces behind the recent National Institute of Mental Health (NIMH) initiative, the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) New Initiatives Conference. This process was started by a conference that led to the identification of seven cognitive domains as important for understanding targets for the treatment of cognition in schizophrenia: speed of processing; attention/vigilance; working memory; verbal learning and memory; visual learning and memory; reasoning and problem solving; and social cognition.[20]

2. Effects of Pharmacological Agents

2.1 Typical Antipsychotic Agents

First-generation or typical antipsychotics are generally effective in treating the positive symptoms of schizophrenia. These medications are not usually associated with reductions in cognitive impairments, although a recent meta-analysis revealed that there were small but detectable improvements in several cognitive domains following treatment with typical antipsychotics.[21] Unfortunately, typical antipsychotics often cause extrapyramidal symptoms that necessitate the use of anticholinergic agents. These agents are associated with global cognitive[22] and memory[23] impairments. Thus, al-

though first-generation antipsychotics have a small beneficial impact on cognition, the necessity of co-medications that adversely impact cognition, as well as severe motor adverse effects, do not indicate that they are effective agents for treating cognitive dysfunction.

2.2 Atypical Antipsychotic Agents

Second-generation or atypical antipsychotics have been shown to have a more beneficial effect on cognitive dysfunction than typical antipsychotics. For example, olanzapine,[24] ziprasidone[25] and risperidone[26] have all been shown to be more effective at treating cognitive deficits than typical antipsychotics. However, direct comparisons between the atypicals have met with mixed results.[15,27] Clozapine appears to improve motor functions better than other atypicals, although it was much less effective than olanzapine and risperidone in improving global cognitive functioning.[4] In addition, psychiatrically stable patients (n = 184) switched to ziprasidone in an open-label study demonstrated improvements in vigilance and executive functions when switched from risperidone, as well as improvements in verbal memory when switched from risperidone or olanzapine.[28] Thus, it appears that atypicals do exert a beneficial effect upon cognitive functioning in individuals with schizophrenia, with specific drugs appearing to impact on different abilities. Unfortunately, as these cognitive improvements are unrelated to changes in other symptoms,[4] finding a balance between the treatment of positive and negative symptoms, as well as cognitive abnormalities, is a difficult task. For instance, development of remission of symptoms, typically viewed as a highly desirable goal for the treatment of schizophrenia, does not guarantee that cognitive improvements will diminish or that functional impairments will abate.

3. Potential Treatment Targets in Schizophrenia

Treatment of the psychotic symptoms of schizophrenia has been focused at blockade of the dopamine D_2 system. Furthermore, much of the research on the neurobiology of schizophrenia has focused on neurotransmitter abnormalities. Not surprisingly, most interventions aimed at cognition have also targeted specific neurotransmitter systems and our review of the previous treatments of the cognitive features of the illness is organised accordingly.

3.1 Agents Targeting the Dopamine System

As noted in section 1, one of the core cognitive dysfunctions seen in individuals with schizophrenia is a severe impairment in working memory. This deficit has been hypothesised to result from a dysregulation of dopamine in the prefrontal cortex (PFC).[19,29] Imagining,[30] post mortem[31] and animal[32] studies have provided evidence for this hypothesis, as has the successful use of amphetamine, a non-selective dopamine agonist, to improve working memory in healthy individuals,[33] but generally only in individuals with poor baseline performance. Although such studies provide evidence of the importance of the dopamine system in this dysfunction, amphetamine is not an appropriate intervention for this population as it has been shown to exacerbate the positive symptoms of schizophrenia.

A recent study[34] reported success in treating cognitive impairments with amphetamine, but again this intervention has limitations as it carries a risk of worsening psychotic symptoms. The results of studies using methylphenidate, another non-selective dopamine agonist, have also been mixed.[29] Goldman-Rakic and colleagues[35] have met with success improving impaired cognition using D_1-receptor agonists such as ABT-431 in monkeys; however, unfortunately there are currently no selective D_1-receptor agonists available for use in humans.[29] Studies of selective D_2-receptor agonists, such as bromocriptine and pergolide, in humans have also met with mixed success.[36-38] Thus, although evidence suggesting that dopamine dysregulation is responsible for many cognitive deficits of individuals with schizophrenia is plentiful, actual interventions targeting this system are not. However, the dopamine system remains a promising avenue for future research.

3.2 Agents Targeting the Adrenergic System

As with the dopamine system, evidence of the impact of the adrenergic system upon cognition is based on results of animal studies. These studies have demonstrated the importance of noradrenaline (norepinephrine) in the functioning of the PFC, one of the brain structures most closely linked to cognitive dysfunction in schizophrenia.[39] In particular, α_2-adrenoceptor agonists, such as clonidine and guanfacine, improved working memory in monkeys and rats. Clonidine and guanfacine also both improved the cognitive performance of individuals with schizophrenia without exacerbating their positive symptoms.[40,41] Unfortunately, clonidine can be heavily sedating and guanfacine can differentially impact cognitive performance depending upon the antipsychotic used.[41] Thus, the efficacy of guanfacine is still an open question. α_1-Andrenoceptors also appear related to cognition as noradrenaline activation of them impairs PFC cognitive functioning during times of stress.[39] While noradrenaline antagonists appear to protect against this during times of stress, administration of these medications does not appear to impact on cognition when an individual is not under stress. Therefore, although animal studies suggest that the adrenergic system also impacts on cognition and specific pharmacological interventions targeting this system are effective in animals and individuals with other psychiatric disorders,[39] the translation of these interventions to the schizophrenic population has been hindered by the adverse effects of the medications, as well as potentially confounding effects of antipsychotic medication.

3.3 Agents Targeting the Acetylcholine System

Cognitive changes in disorders such as Alzheimer's dementia and Parkinson's disease have been correlated with central cholinergic dysfunction, leading to the hypothesis that this system might be important for understanding the cognitive profiles of individuals with schizophrenia.[42] Although post mortem examinations have not demonstrated the same gross neuropathological evidence as these other disorders, there is evidence of decreased muscarinic[43] and nicotinic[44] receptors in the brains of individuals with schizophrenia. The investigation of the impact of acetylcholinesterase inhibitors and muscarinic agonists on cognition has been hindered by the occurrence of severe gastrointestinal adverse effects with most medications of this type.[42] Galantamine, an acetylcholinesterase inhibitor, has shown efficacy in one study,[45] although further examination is warranted as subjects in this study were excluded based upon neurological factors, which may have accounted for cognitive improvements. Donepezil, another acetylcholinesterase inhibitor, has also met with mixed results[42] and three randomised trials have failed to show positive results. Finally, rivastigmine also yielded negative results in a very recent study, suggesting again that the currently available treatments lack efficacy on cognition.[42] Thus, although there is evidence of the involvement of the acetylcholine system in the cognitive dysfunction of individuals with schizophrenia, there are to date no effective treatments resulting from this area of research.

3.4 Agents Targeting the Serotonin System

Several atypical antipsychotics that are modestly successful in improving the cognition of individuals with schizophrenia specifically target the serotonin (5-HT) receptors, leading to the hypothesis that this system may be an appropriate avenue for specific pro-cognitive interventions.[46] Unfortunately, there is a lack of agreement as to whether individual 5-HT-receptor activation or antagonism will be effective in augmenting cognition and the interactions of the serotonin system are among the most complex of any well understood transmission system. Evidence from animal models suggests that 5-HT_{1A}-receptor partial agonists, 5-HT_{2A}-receptor antagonists, 5-HT_4-receptor partial agonists and 5-HT_6-receptor antagonists all have the potential to improve cognition, although none have been tested in humans.[46] One previous study reported beneficial effects from a serotonergic intervention, tandospirone, a 5-HT_{1A}-receptor agonist.[47] However, only a limited cognitive assessment was reported in

that study and the sample size was modest. Thus, while this appears very promising, this finding will have to be replicated with a larger study.

3.5 Agents Targeting Other Neurotransmitter Systems

Models based on basic science research have also been developed that identify other neurotransmitter systems, such as the GABA,[48] the glutamate AMPA (alfa-amino-3-hydroxy-5-methyl-4-isoxazole, propionic acid)[49] and NMDA receptor subsystems.[50] Although these hypotheses have supporting evidence, there have been no substantial successes and several failures targeting cognitive symptoms within these systems. There are several lines of research evaluating these treatments, including interventions aimed at glutamate receptor subsystems and at the GABA system as well.

3.6 Cognitive Remediation: a Successful Intervention

Although pharmacological interventions have met with mixed results at best, behavioural interventions have demonstrated a significantly beneficial effect on the cognitive dysfunction of schizophrenic individuals. These approaches, which are referred to as cognitive remediation or cognitive enhancement, use techniques from the fields of clinical neuropsychology and rehabilitation and focus on the acquisition of cognitive skills. In one study, individuals who received cognitive training, in conjunction with a supportive employment programme, showed improvements in cognition, as well as greater treatment compliance, fewer depressive symptoms, more working hours and higher wages than individuals in a supportive employment programme who did not receive cognitive training.[51] Wexler and Bell,[52] among others,[53,54] also report improvement of both symptoms and outcome following cognitive remediation.

Cognitive remediation generally takes the form of computerised cognitive exercises that increase in difficulty over time and that focus on areas most impaired in individuals with schizophrenia, such as attention and concentration, psychomotor speed, learning and memory, and executive functions.[51] Some programmes, such as the one used by Wexler and Bell,[52] are designed to cover areas in which patients have better baseline skills more quickly and to focus patients' training on areas of greater impairment. Training typically ranges from two to six sessions, each of 45 minutes' to 1 hour's duration, for approximately 12 weeks.

While these interventions are often very labour intensive and unlikely to be available to large numbers of patients with schizophrenia in the near future, their results make a critical point: cognitive impairment is not an intractable target. If pharmacological interventions have failed, it is not because cognitive impairment cannot be modified under any circumstances. It is possible that several features of previous studies, in addition to the medications themselves, may have led to less promising results.

4. Limitations of Pharmacological Studies

The lack of pharmacological interventions to treat the cognitive dysfunction of individuals with schizophrenia, in spite of research threads that appear theoretically well founded and within basic science investigations, is particularly puzzling in light of the success of behavioural interventions. There are several potential reasons to explain the failure of these basic science models to translate into effective treatments.

The first possible explanation relates to potential flaws within the medications themselves. Animal studies often utilise direct administration to the CNS; however, these medications may not cross the blood-brain barrier and may therefore lose their efficacy when administered orally. Other medications, such as some nicotinic agonists, have very short half-lives or lead to rapid receptor sensitisation, which quickly reduces their efficacy.

A second possible reason for the lack of efficacy of drugs targeting these abnormalities has to do with flaws inherent in the experimental designs used in the previously discussed studies. In a review of studies examining the effect of atypical antipsychotics on cognition, Harvey and Keefe,[55] for example,

noted that variability between studies and methodological flaws make it difficult to compare across findings or to make definitive statements about a single medication. Many studies are limited by small sample sizes, high attrition and short duration.[56] Studies that are limited in duration risk missing effects that could be observed with longer treatment durations.[55]

Another potential explanation relates to dose administration effects. Both Mishara and Goldberg[21] and Harvey and Keefe[55] noted that dosages of both typical and atypical medication were higher in the literature than those recommended in clinical practice. This discrepancy is particularly problematic as the relationship between cognitive functions and dopamine function has been found to exhibit an inverted-U response in that the optimal effect is received from a median dosage, with either too much or too little medication failing to have an impact.[29] This inverted-U has also been found in increasing dosages of cholinomimetic drugs in animal studies.[42] Thus, studies that utilise a medication dosage that is too high may not find a statistically significant effect even if there is a clinical relationship.

A fourth potential explanation for the lack of translation from basic science to treatment relates to the utilisation of healthy volunteers as intermediaries between basic science studies and clinical trials. The cognitive deficits seen in individuals with schizophrenia are almost certainly the result of abnormalities in multiple neurotransmitter systems or even other aspects of brain circuitry.[29] Thus, medication-induced cognitive deficits, which may be confined to a specific neurotransmitter system, may be ameliorated by a pharmacological intervention that targets a specific site of action. Finding this relationship does not necessarily indicate that this agent will be effective in alleviating symptoms that are the result of complex interactions between multiple systems. Furthermore, the effects of antipsychotic medication may confound the impact of specific pro-cognitive medications.[41] It is very unlikely that treatments that are ineffective at enhancing cognition in people who are medicated and effective only in those patients with schizophrenia who are not treated with antipsychotic medications will ever be suitable. However, it is possible that such an intervention would be useful for individuals who are in the prodrome of the illness.

Finally, the failure of these agents to alleviate cognitive dysfunction with the schizophrenic population may in fact reflect a lack of adequate outcome measures rather than a lack of medication effects. There is tremendous variability within the literature both in terms of outcome measures chosen and guidelines for determining both impairment and improvement.[55] Although neuropsychological measures have been seen as the gold standard because of their reliability and validity, as well as their norms for 'normal' performance, several of these important tests lack alternate forms and thus improvements cannot easily be separated from practice effects.[55] Additionally, it is unclear whether these measures are the best tools for approximating gains in real-world functional outcome, which is the ultimate goal of all cognitive enhancing interventions.

5. Suggestions for Future Research

As pharmacological interventions targeting cognitive dysfunction of individuals with schizophrenia are developed and refined, careful attention should be paid to the methodology and research design of studies examining the efficacy of these medications. Harvey and Keefe[55] offer several guidelines for designing experiments that are more likely to yield both statistically significant and meaningful results.

Furthermore, outcome variables should be chosen with care. Although there is a clear relationship between cognitive performance and functional outcome, repeated presentations of neuropsychological inventories may not be the best means for capturing true therapeutic change. Possible refinements of informant ratings of real-world outcome variables would be a good alternative, as being rated by an informant is not as vulnerable to practice and exposure effects as cognitive testing. There are several promising measures that are designed for informant ratings, such as the Specific Level of Functional scale.[57] In addition, it is important for researchers

to attend to the difference between statistical significance and clinical significance. For example, variables with a small effect size may lead to statistically significant results if the sample is large enough, but this may not translate into meaningful changes within individuals' cognitive functioning. One of the recommendations of the MATRICS was the inclusion of a function-based assessment as an outcome variable in all clinical trials of cognitive enhancing treatments.[20] We also recommend that function-based assessments be included in future examinations of the effectiveness of pro-cognitive treatments. Such assessments may also provide vital information about factors that may impact the relationship between cognitive change and improvements in functioning.

Finally, as behavioural and cognitive remediation interventions appear so promising, we recommend that they be included as augmenting aspects of future clinical trials. The inclusion of both pharmacological and behavioural interventions may exert a combined effect in terms of functional outcome that far exceeds the impact of either of these if offered alone. Additionally, behavioural interventions may help individuals with schizophrenia to learn new mechanisms for adaptive functioning, bridging the gap between improved cognition and real-world functioning.

6. Conclusions

Over the last decade, cognitive dysfunctions have emerged as an important intervention target for individuals with schizophrenia. Although basic science models and examinations of healthy individuals have suggested several promising areas of potential intervention, there has been a lack of success translating these veins of research into effective treatments. Behavioral interventions have met with more success and, in combination with pharmacological interventions, are a promising area for future research that will hopefully alleviate the cognitive dysfunction associated with schizophrenia.

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Correspondence and offprints: Dr *Philip D. Harvey*, Department of Psychiatry, Mount Sinai School of Medicine, 1425 Madison Avenue, Room L4-42, New York, NY 10029, USA. E-mail: philipdharvey1@cs.com